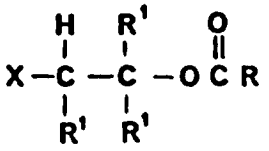
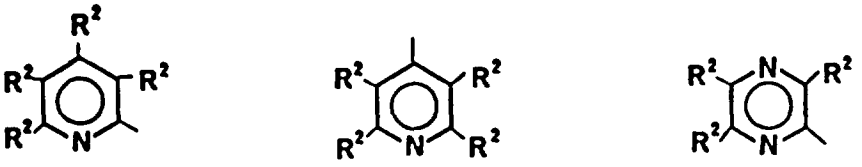
# HETEROCYCLIC ESTERS AS RELEASE AGENTS FOR CARBOXYLIC ACID FLAVORANTS

This invention establishes novel esters of heterocyclic ethanol derivatives as carboxylic acid flavorant release compounds of the structural formula:



where x is a heterocyclic radical represented by the chemical structures:

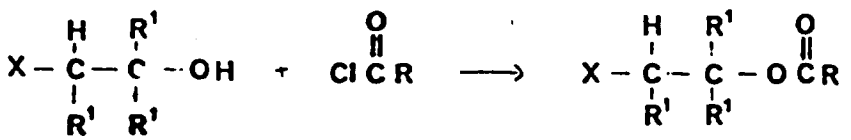


R is aromatic, alicyclic, or aliphatic hydrocarbon radical containing between 3 to about 10 carbon atoms

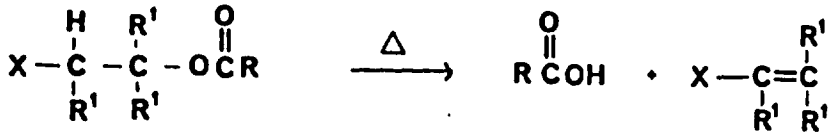
$R^1$ is H, aliphatic, alicyclic, aromatic, or heterocyclic

$R^2$ is H or alkyl.

These novel esters can be prepared by reacting the appropriate heterocyclic ethanol derivatives with one equivalent of a desired acid chloride. The salt if formed is neutralized yielding the product in good yield. The product is easily purified by distillation and chromatographic means.



The above esters are stable compounds and are odorless. However, when heated at relatively low temperature, such as 250°C, they decompose to release the carboxylic acid flavorant in good yield.



Carboxylic acids are known tobacco flavorants, for example: isovaleric acid and 3-methylvaleric acid (R H. Stedman, and C. P. Stills, U.S. Patent 3180340). However, their low odor threshold may prevent their use in sufficient amounts, particularly in low delivery cigarettes. The esters described above can be used alone or in conjunction with a carboxylic acid flavorant to allow for reduction or elimination of the rod odor.

A variety of methods that release carboxylic acid flavorants on pyrolysis have been described in the patent literature. For example, U.S. Patent 2,766,145 described the use of esters of monosaccharides, disaccharides, and derivatives of malonic acid. U.S. Patent 2,766,150 addressed the problem by the use of synthetic polymers.

The numerous methods which are known to release carboxylic acid flavorants are not completely satisfactory. The major disadvantages include insufficient release of the flavorant on pyrolysis and, in the case of polymers, insufficient solubility for application on tobacco.

A review of the literature revealed that esters of 2-(2-hydroxyethyl)pyridine have previously been synthesized. Susan deBurgh Norfolk et al. synthesized 2-(2-pyridyl)ethyl acetate for use in a mechanistic study dealing with the pyrolysis of esters. Also Kornfeld and Houminer synthesized 2-(2-acetoxy-

2-phenylethyl)-3,5,6-trimethylpyrazine to illustrate the necessity of the hydroxy group in the mechanism they postulated to be occurring in their study.

U.S. Patent 2,766,145 described the use of heterocyclic esters, such as furane, thiophene, pyridine, pyrrole, pyrone, and indoles, represented by furfuryl isovalerate, as carboxylic acid release agents for the use in smoking articles. However, esters of heterocyclic ethanol derivatives were not included as examples and we find them to have a major advantage over esters represented by furfuryl isovalerate, as will be demonstrated below.

Furfuryl acetate (Example I) was synthesized according to the procedure described by O'Brian in U.S. Patent 2,766,145. On pyrolysis under our normal conditions (Example VIII) it was found to be unreactive, with no release of the isovaleric acid. Also, 2-(1-(3-methylvaleryloxy)methyl)pyridine (Example II) was prepared and on pyrolysis, no release of 3-methylvaleric acid was observed.

However, the heterocyclic ethanol esters described in this invention, for example: 2-(2-(3-methylvaleryl)ethyl)pyridine (Example III), were synthesized and found to undergo smooth thermolysis (Example VIII) to release, in this case, 3-methylvaleric acid in good yield. Similar results were obtained for other esters derived from pyridine and pyrazineethanols, as illustrated in the examples. This concept should also be applicable to heterocyclic ethanol derivatives of thiazole, oxazole, imidazole, furan, pyrrole, thiophene and the like.

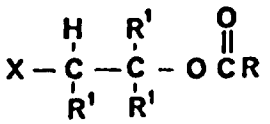
In addition, a number of vinyl heterocycles are tobacco identical, for example: 2-ethyl-6-vinylpyrazine (R. A. Wilson, B. D. Mookherjee, and J. F. Winall, IFF Presentation at Philip Morris 1982), thus enabling a combination of tobacco identical and non-tobacco identical components. This versatility in components would also allow design of systems which have desirable synergistic subjective responses.

It can be concluded from the above information that esters derived from heterocyclic ethanol derivatives have a major advantage over the esters, represented by furfuryl acetate, described in U.S. Patent 2,766,145.

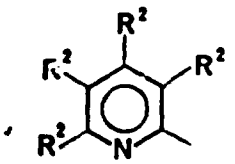
It is the main object of this invention to provide novel esters of heterocyclic ethanol derivatives which are stable and non-volatile under conditions of storage and effectively release carboxylic acid flavorants into the mainstream and sidestream of a burning cigarette upon smoking.

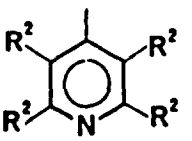
We suggest claiming:

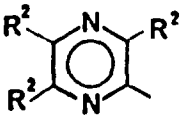
1. Compounds of the general formula:



where x is a heterocyclic radical represented by the chemical structures:







R is aromatic, alicyclic, or aliphatic hydrocarbon radical containing between 3 to about 10 carbon atoms

$R^1$ is H, aliphatic, alicyclic, aromatic, or heterocyclic

$R^2$ is H, or alkyl.

2. 2-(2-(3-Methylvaleryloxy)ethyl)pyridine.

3. 4-(2-(3-Methylvaleryloxy)ethyl)pyridine.

4. 2-(2-Cyclohexylcarbonyloxy-4-methylpentyl)-3,5,6-trimethylpyrazine.

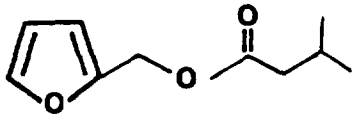
5. 2-(2-Isovaleryloxy-4-methylpentyl)-3,5,6-trimethylpyrazine.

6. 2-(2-(3-Methylvaleryloxy)-2-phenylethyl)pyrazine.

7. Smoking compositions of the above.

## EXAMPLE I

## Furfuryl Isovalerate

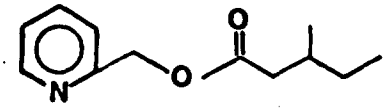


A solution of 7.1g (0.061 moles) of isovaleryl chloride in 100 ml of ether was cooled to 0°C. Furfuryl alcohol (6.0g, 0.061 moles) in 40 ml of ether was added dropwise. Stirring was continued for approximately 15 minutes while maintaining the temperature of 0°C, then 18-24 hours at room temperature. The reaction product was diluted with water and extracted with ether. The ether layer was washed with aqueous saturated sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yielded a liquid, which was distilled in vacuo to give 7.0g of a light yellow oil.

NMR and IR confirm the above structure.

## EXAMPLE II

## 2-(1-(3-Methylvaleryloxy)methyl)pyridine



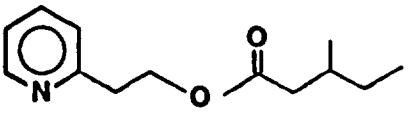
A solution of 7.3g (0.054 moles) of 3-methylvaleryl chloride in 100 ml of ether was cooled to 0°C. 2-Pyridylcarbinol (5.9g, 0.054 moles) in 40 ml of ether was added dropwise. Stirring was continued for approximately 15 minutes while maintaining the temperature at 0°C, then 18-24 hours at room temperature. An equal volume of aqueous saturated sodium bicarbonate was added and the solution was allowed to stir for 15 minutes to 12 hours until neutralization of the salt was complete. The organic layer was washed with aqueous saturated sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yielded a liquid. The liquid was purified by preparative thin layer chromatography on silica gel using 10% ethyl acetate/hexane as the eluent. 6.7g of the product was obtained as an oil.

NMR and IR confirm the above structure.

Analysis; calculated for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.63; H, 8.19; N. 6.68.

## EXAMPLE III

## 2-(2-(3-Methylvaleryloxy)ethyl)pyridine



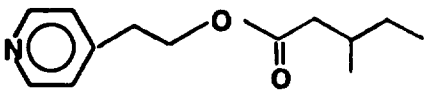
The synthesis of the title compound was conducted on a 0.045 mole scale using the same conditions as described in Example II. The liquid was purified by vacuum distillation, b.p. 71-73°C/0.01 mm Hg, yield 5.9g.

NMR and IR confirm the above structure.

Analysis; calculated for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.42; H, 8.66; N, 6.21.

## EXAMPLE IV

## 4-(2-(3-Methylvaleryloxy)ethyl)pyridine



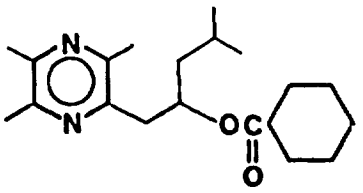
The synthesis of the title compound was conducted on a 6.9 mmole scale using the same conditions as described in Example II. The liquid was purified by preparative thin layer chromatography on silica gel using ethyl acetate/hexane 1/15 as the eluent. 50 mg of the pure product was isolated as an oil.

NMR and IR confirm the above structure.

Analysis; calculated for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.53; H, 8.63; N, 6.43.

EXAMPLE V

2-(2-Cyclohexylcarbonyloxy-4-methylpentyl)-3,5,6-trimethylpyrazine



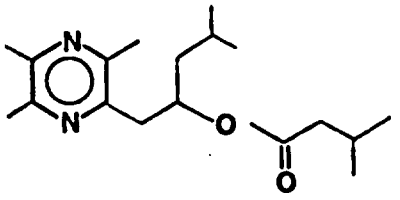
To a supension of 50% sodium hydride (0.23g, 9.5 mmoles) in benzene was added 1.0g (4.5 mmoles) of 2-(2-hydroxy-4-methylpentyl)-3,5,6-trimethylpyrazine in 10 ml of benzene. The mixture was heated to 70°C for 30 minutes, then allowed to cool to room temperature. A solution of 0.66g (4.5 mmoles) of cyclohexylcarboxylic acid chloride in 10 ml of benzene was added and the mixture was stirred at room temperature for 18-24 hours. Ether and water were added and the organic layer was washed with water followed by aqueous saturated sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent under reduced pressure yielded a residue. The residue was purified by preparative thin layer chromatography on silica gel using 20% ethyl acetate/hexane as the eluent. 800 mg of the product was obtained as an oil.

NMR and IR confirm the above structure.

Analysis; calculated for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.00; H, 9.69; N, 8.59.

## EXAMPLE VI

## 2-(2-Isovaleryloxy-4-methylpentyl)-3,5,6-trimethylpyrazine



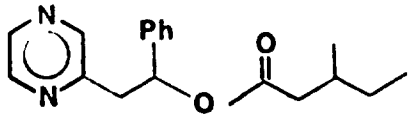
The synthesis of the title compound was conducted on a 4.5 mmole scale using the same conditions as described in Example V. 700 mg of pure product was obtained as an oil.

NMR and IR confirm the above structure.

Analysis; calculated for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.48; H, 9.77; N. 9.00.

## EXAMPLE VII

## 2-(2-(3-Methylvaleryloxy)-2-phenylethyl)pyrazine




The synthesis of the title compound was conducted on a 8.1 mmole scale using the conditions described in Example V. 1.4g of pure product was obtained as an oil.

NMR and IR confirm the above structure.

## EXAMPLE VIII

## Pyrolysis of I-VI at 250°C

A 10-50 mg sample of each of the above compounds were pyrolyzed in a sealed tube at 250°C for 10 minutes. The yield of the released carboxylic acid flavorant in each case was determined by GC. The following table summarizes the results.

| Compound | Flavor | Yield % |
|---|---|---|
| I | Acetic Acid | 0 |
| II | 3-Methylvaleric Acid | 0 |
| III | 3-Methylvaleric Acid | 85 |
| IV | 3-Methylvaleric Acid | 93 |
| V | Cyclohexane Carboxylic Acid | 50 |
| VI | Isovaleric Acid | 95 |

## EXAMPLE IX

### Smoking Composition Containing a Flavorant Compound

Cigarettes were fabricated employing tobacco treated with an ethanolic solution between 0.01 and 2 weight percent, based on weight of the smoking composition of 2-(2-(3-methylvaleryloxy)ethyl)pyridine. Untreated controls were prepared using the identical tobacco and the treated cigarettes were compared to the control by an experimental smoking panel. The treated cigarettes were found to have increased flavor amplitude.